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# Comparison of $^{99m}$Tc-sestamibi lung/heart ratio, transient ischaemic dilation and perfusion defect size for the identification of severe and extensive coronary artery disease

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**Abstract.** The ability to identify patients with severe coronary artery disease (CAD) by analysis of perfusion defects is limited. The lung/heart ratio (LHR) and transient ischaemic dilatation (TID) have been used for this purpose in thallium-201 scintigraphy. The value of these parameters in technetium-99m sestamibi single-photon emission tomography (SPET) imaging is controversial. In this study, therefore, we determined TID and LHR in a single-day rest/stress $^{99m}$Tc-sestamibi SPET perfusion protocol and compared these measurements with perfusion defect size (PDS) and angiographic severity of CAD. Severe CAD was defined as >75% left main coronary stenosis and/or >90% proximal left anterior descending artery stenosis and/or >90% proximal stenosis in the left circumflex and right coronary arteries. LHR was determined from a stress anterior planar image recorded ≤6 min after exercise. TID ratio was derived from automatically calculated left ventricular rest/stress volumes, and PDS was measured based on semi-automated computer software (CEqual). Diagnostic accuracy and predictive values were compared between 22 patients with severe and 98 patients without severe CAD. LHRs showed a higher sensitivity (73%) for the assessment of severe CAD as compared to PDS and TID ratio (41% and 23% respectively, $P<0.01$), whereas specificity was highest for TID ratio [95%, $P<0.01$ when compared to PDS (84%) and LHR (82%)]. It is concluded that increased LHR in $^{99m}$Tc-sestamibi myocardial perfusion imaging seems to yield good diagnostic accuracy in the detection of patients with severe CAD and may be derived from a single-day rest/stress study.

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## Introduction

The ability to define the severity of coronary artery disease (CAD) non-invasively using technetium-99m sestamibi myocardial perfusion scintigraphy is not well documented but is clinically important. Transient ischaemic LV dilation (TID) has been proposed as a marker of exercise-induced left ventricular dysfunction, and increased lung uptake [measured as lung/heart ratio (LHR)] has been established as a prognostic marker in thallium-201 perfusion imaging, but its role in $^{99m}$Tc-sestamibi imaging is not yet clear. In this study, therefore, we determined TID and LHR in a single-day rest/stress $^{99m}$Tc-sestamibi single-photon emission tomography (SPET) perfusion protocol and compared these measurements with perfusion defect size and angiographic severity of CAD.

## Materials and methods

Among 849 patients referred for $^{99m}$Tc-sestamibi myocardial perfusion scintigraphy, we identified 120 in whom coronary angiography was performed within 3 months of the perfusion study and documented significant coronary stenoses (>50% of at least one epicardial artery) without any coronary events or interventions between the two procedures and without left bundle branch block, severe non-ischaemic heart disease or a left ventricular ejection fraction <0.45.

For the definition of normal values, we identified 38 control subjects who had a very low pretest probability of CAD and no evidence of other heart disease.

Severe disease was defined as >75% left main coronary stenosis and/or >90% proximal left anterior descending artery stenosis and/or >90% proximal stenosis of the left circumflex and right coronary arteries (same grading as in reference [1]). Twenty-two patients met these criteria. The remaining 98 patients were classified as having less severe coronary disease.

All patients were studied with a same-day rest/stress study at least 4 h apart [2]. The rest SPET studies were acquired in the morning, 1 h after injection of the radiotracer [296–444 MBq (8–12 mCi) of $^{99m}$Tc-sestamibi], followed by a symptom-limited bicycle ergometer test with ECG monitoring in the afternoon. Beta-blocker medication was discontinued in most patients. One minute before completion of the exercise test, 814–962 MBq (22–26 mCi) of $^{99m}$Tc-sestamibi was injected. After a short cool-down period of 4–6 min, an anterior planar image of the chest was obtained containing a minimum of 1 million counts. Immediately thereafter, a 180° non-circular SPET study was performed, using 16 stops at 45–60 s with a dual-head camera and 90° orientation (Vertex, ADAC), resulting in 32 image data sets. Image processing was performed in all patients using a backprojection algorithm without scatter or attenuation correction and a Butterworth filter with a cut-off value of 0.4 and an order of 10.

Image interpretation was done visually supported by quantitative analysis software (CEqual) by two observers (C.G. and M.R.) without knowledge of the angiographic findings. Images were classified as showing ischaemia (reversible defect), scar (fixed defect) or both. Ischaemia was defined as severe when it involved ≥15% of the left ventricle (PDS post stress minus PDS at rest)

The LHR was determined from an anterior immediate post stress planar image using a nine-pixel rectangular region of interest placed over the maximal myocardial and left lung activity based on visual inspection. LHR was calculated by the formula LHR=[lung activity/heart activity].

TID ratios were derived from an automated computer program using ungated SPET studies [3]. This program segments the left ventricle, estimates and displays the endocardial surface, the pericardial surface and the valve plane for both the rest and the stress set, calculates the endocardial volumes (Vol) (bounded by the endocardial surface and the valve plane) and derives the transient ischaemic dilation (TID) ratio as [TID ratio=Vol stress/Vol rest].

Perfusion defect size (PDS) was derived from stress SPET images using an FDA-approved computer program (CEqual). After operator definition of the left ventricular apex and base, PDS was calculated displaying PDS at rest, PDS after stress and its match or mismatch on a polar map. A global PDS >30% of the left ventricle was defined as an indicator of severe and extensive CAD.

The upper limits of normal LHR and TID were determined as the mean +2 standard deviations of the values observed in control subjects. Relative sensitivity and specificity for the identification of patient groups were analysed. Chi square analysis was used for comparison of categoric variables. A $P$ value of ≤0.05 was considered to represent statistical significance. Intra-observer variability in respect of LHR, TID and PDS was tested in 18 patients selected for a large range of initial values.

## Results

In the control group, TID ratios ranged between 0.75 and 1.15 with a mean of 0.96±0.11. Thus, the upper limit of normal was defined as 1.18 (mean+2SD). Values for LHR ranged between 0.28 and 0.45 with a mean of 0.37±0.05. Values for men were significantly higher than those for women (0.38±0.12 vs 0.36±0.10, $P$=0.049). Therefore, upper limits of normal were defined as 0.51 for male and 0.47 for female patients. In this control group, mean rest volumes were 63±18 ml and mean stress volumes were 60±19 ml. Intra-observer variability in respect of TID ratios was 0.00 (fully automated procedure); intra-observer variability in respect of LHR and PDS was 0.02±0.03 and 4.0%±3.5%, respectively.

Abnormal LHR, abnormal TID ratio and both PDS parameters (a global PDS >30% and a reversible PDS ≥15%) were significantly more frequent in patients with severe CAD (Tables 1, 2 and 3). In these patients, an abnormal LHR was found in 16/22 patients (73%), an ab-

**Table 1.** Clinical, exercise test and angiographic data

| | CAD severity[a] | | $P$ value |
|---|---|---|---|
| | Severe | Less severe | |
| No. of patients | 22 | 98 | |
| Male patients (%) | 91 | 76 | NS |
| Mean age (mean±1SD) | 55±19 | 56±13 | NS |
| History of myocardial infarction (%) | 55 | 45 | NS |
| Typical angina (%) | 50 | 46 | NS |
| Limiting dyspnoea (%) | 50 | 22 | <0.01 |
| Use of beta-blockers (%) | 64 | 54 | NS |
| Watt <85% of predicted value (%) | 68 | 35 | NS |
| Heart rate <85% of predicted value (%) | 77 | 63 | NS |
| Rate-pressure product ratio <2.0 (%) | 32 | 18 | NS |
| Exercise duration <6 min (%) | 32 | 24 | NS |
| Significant ST deviation (%) | 77 | 55 | NS |
| Ejection fraction <60% (%) | 32 | 20 | NS |
| Triple-vessel disease (%) | 91 | 26 | <0.01 |

[a] As defined for this study: see Materials and methods

**Table 2.** Results from scintigraphy

| | CAD severity[a] | | $\chi^2$ | *P* value |
|---|---|---|---|---|
| | Severe | Less severe | | |
| No. of patients | 22 | 98 | | |
| Ischaemia present (%) | 50 | 34 | | NS |
| Severe ischaemia present (%)[b] | 41 | 19 | 4.61 | <0.05 |
| Normal perfusion on stress image (%) | 0 | 9 | | NS |
| Scar only (%) | 9 | 11 | | NS |
| Ischaemia and scar (%) | 41 | 46 | | NS |
| PDS >30% (%) | 41 | 16 | 6.53 | <0.01 |
| Pathological LHR (%) | 73 | 18 | 25.93 | <0.01 |
| Pathological TID ratio (%) | 23 | 5 | 7.25 | <0.01 |

[a] As defined for this study: see Materials and methods
[b] Defined by CEqual, ≥15% of left ventricle

**Table 3.** Accuracy of scintigraphic markers for the detection of severe CAD

| | LHR | PDS>30% | TID | *P* value |
|---|---|---|---|---|
| Sensitivity | 73 | 41 | 23 | <0.01* |
| Specificity | 82 | 84 | 95 | <0.01** |
| Positive predictive value | 47 | 63 | 50 | NS |
| Negative predictive value | 93 | 86 | 84 | NS |
| Accuracy | 80 | 76 | 81 | NS |

LHR, Lung/heart ratio; PDS, perfusion defect size; TID, transient ischaemic dilation ratio
**P*<0.01 for LHR vs PDS and TID ratio; ***P*<0.01 for TID ratio vs PDS and LHR

normal TID ratio in 5/22 (23%), a global PDS >30% in 9/22 (41%) and a reversible PDS ≥15% (representing severe ischaemia) in 9/22 (41%). In contrast, in patients with less severe CAD, these findings were obtained in 18/98 (18%), 5/98 (5%), 16/98 (16%) and 19/98 (19%) patients, respectively.

LHR was the most sensitive marker of severe CAD (73% vs 41%, 41% and 23% for a reversible PDS ≥15%, a global PDS >30% on stress images and TID ratio, respectively) while TID ratio was the most specific finding. Consequently the negative predictive value for severe CAD was best for LHR (93% vs 86%, 87% and 84% for the two PDS criteria and the TID ratio) (Table 3).

## Discussion

This is, to our knowledge, the first study to assess the ability of three different scintigraphic markers to detect angiographically defined severe CAD using a same-day $^{99m}$Tc-sestamibi myocardial perfusion scintigraphy protocol. In this study, using immediate post stress imaging for the assessment of the LHR and an automated border detection algorithm for the calculation of transient ischaemic dilation in $^{99m}$Tc-sestamibi imaging, we could demonstrate that LHR and TID correlated significantly with the angiographic severity of CAD in patients with normal or mildly decreased left ventricular function. The comparison of LHR, TID and PDS analysis showed that LHR was the most sensitive parameter for the identification of patients with severe disease in our study population, while TID showed a low sensitivity but a high specificity.

LHR derived from $^{99m}$Tc-sestamibi perfusion studies is an indirect measure of left ventricular dysfunction and generally becomes abnormal in patients with decreased ejection fraction induced by physical exercise [4, 5]. In order to exclude possible "confounders" in this respect, patients with a resting ejection fraction <45%, with non-ischaemic heart disease and/or with left bundle branch block were not included in the present study. In contrast to the present findings, LHR derived from stress $^{99m}$Tc-sestamibi imaging was found to have a poor sensitivity for the detection of severe CAD in a previous study [6]. In that study, however, LHR was most likely measured too late (e.g. ≥1 h after physical exercise), since recent studies have shown that clinically important wash-in to the heart [7] and wash-out from the lungs [8] may occur in patients imaged 60–120 min after $^{99m}$Tc-sestamibi injection.

In accordance with findings by Mazzanti et al. [1], we could confirm a high specificity for TID ratios in patients with severe and extensive CAD defined by angiography (specificity was 95% both in our study and in that by Mazzanti et al.). The reason for the lower sensitivity of TID ratios in our study (23%) as compared to the sensitivity reported for patients imaged with the dual-isotope protocol (72%) [1] may lie in differences in acquisition protocols, radiotracers, filter techniques and patient selection.

PDS derived from $^{99m}$Tc scintigraphy has been shown to have prognostic implications for patients with CAD [9]. To our knowledge, data comparable to those obtained in our study regarding the ability of PDS to detect severe and extensive CAD have not previously been published for $^{99m}$Tc-sestamibi perfusion studies. As reported from studies using $^{201}$Tl myocardial perfusion imaging, high-risk CAD patterns (e.g. left main disease pat-

tern) are detected in only about 14% of these patients [10]. We found PDS to have a good specificity (84%) but limited sensitivity (41%) for the detection of patients with severe CAD when analysing global perfusion defects in stress images.

This study has some limitations:

1. The presence of multiple perfusion defects indicative of multi-vessel CAD was not separately analysed in this study.
2. We used the same angiographic definition for severe disease as other authors in a similar study [1]; however, these definitions, as well as the visual assessment of the degree of stenosis, remain arbitrary and are far from providing a gold standard classification.

In conclusion, we could demonstrate that in $^{99m}$Tc-sestamibi imaging, as in $^{201}$Tl studies, the lung/heart ratio, assessed early after exercise, and transient ischaemic dilation can be used as markers of severe and extensive CAD. These parameters add helpful information to the analysis of perfusion defect size, but their prognostic impact over other available markers of severe and extensive CAD remains to be determined.

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